well as in isolated Langendorff-perfused hearts. In both cases heart rate was ~22% lower ($p<0.05$) in CIO mice suggesting iron-overload impairs SAN electrical activity. Indeed, spontaneous action potential (AP) frequency was reduced by 34% ($p<0.05$) in isolated SAN myocytes from CIO mice along with a reduction ($p<0.05$) in slope of the diastolic depolarization from 35.1 ± 3.6 V/s in controls to 18.8 ± 2.2 V/s in CIO. The maximum diastolic potential was unaltered in CIO myocytes. Voltage-clamp experiments showed that the reduction in SAN firing frequency was linked to a reduction ($p<0.05$) in L-type Ca^{2+} current ($I_{Ca,L}$) density from -4.8 ± 0.8 pA/pF to -2.6 ± 0.2 pA/pF along with a right shift ($p<0.05$) in the $V_{1/2}$ for activation from -20.2 ± 3.7 mV in control to -6.2 ± 2.6 mV in CIO SAN myocytes. In conclusion, the severe bradycardia caused by iron-overload originates from impaired intrinsic electrical activity and reduced $I_{Ca,L}$ in SAN pacemaker myocytes.

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Sex Hormones And β_2-adrenergic Stimulation Regulate Slow Delayed-rectifier Potassium Current In Control And Heart Failure Rabbits

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Little is known about sex differences in slow delayed-rectifier potassium current (I_{Ks}) in response to β-adrenergic stimulation.

Here, we assess the role of sex hormones on I_{Ks} in response to β_1- & β_2-AR stimulation in control and heart failure (HF) rabbits. I_{Ks} in control male increased in response to isoproterenol (ISO, 500nM) (at +50mV, Step: 1.07 ± 0.10 to 1.79 ± 0.23 pA/pF; Tail: 0.57 ± 0.04 to 0.93 ± 0.07 pA/pF, $p<0.05$), an effect blocked by β_2-AR antagonist ICI-118,551,150 nM (at +50mV, Step: 1.16 ± 0.14 pA/pF; Tail: 0.61 ± 0.06 pA/pF), but not by β_1-AR antagonist CGP-20712A, 300nM. I_{Ks} in control female was significantly less ($p<0.01$) than control male, but did not increase with ISO (at +50mV, Step: 0.62 ± 0.04 to 0.71 ± 0.04 pA/pF; Tail: 0.35 ± 0.02 to 0.41 ± 0.03 pA/pF). After castration, I_{Ks} in control male did not change with ISO (at +50mV, Step: 0.89 ± 0.07 to 1.10 ± 0.11 pA/pF; Tail: 0.50 ± 0.03 to 0.62 ± 0.05 pA/pF, p=NS), and after ovariectomy, I_{Ks} in control female now showed enhancement with ISO (at +50mV, Step: 0.74 ± 0.06 to 1.27 ± 0.09 pA/pF; Tail: 0.41 ± 0.03 to 0.72 ± 0.05 pA/pF,$p<0.01$ (a 72% increase in I_{KS} step comparable to the 64% increase in I_{Ks} step in control male)). With HF, sex differences in I_{Ks} responsiveness to ISO went away. HF male exhibited reduced I_{Ks} (vs control male) but I_{Ks} did not enhance with ISO (at +50mV, Step: 0.46 ± 0.02 to 0.50 ± 0.03 pA/pF; Tail: 0.28 ± 0.01 to 0.30 ± 0.01 pA/pF,p=NS). HF female still showed no significant I_{Ks} enhancement with ISO (at +50mV, Step: 0.61 ± 0.06 to 0.76 ± 0.11 pA/pF; Tail: 0.34 ± 0.03 to 0.42 ± 0.05 pA/pF, p=NS). Thus, there are important sex differences in β-AR stimulation of I_{Ks}, that are mediated by β_2-AR, and which are modulated by sex hormones. With HF, sex differences in basal I_{Ks} and its alterations during HF may underlie sex-based differences in arrhythmogenicity.

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More Effective and Safer Cardiac Electric Stimulation Using Multidirectional and Biphasic Stimuli

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Because the ability of electric fields to excite cardiac cells depends on stimulus direction, effective *in situ* cardiac stimulation requires relatively high stimulus amplitude. However, high-strength fields may cause electroporation and cell injury. In this study, we compared the effectiveness of unidirectional (US) and multidirectional stimulation (MS) in 16 populations of isolated, randomly-oriented cardiomyocytes. MS was achieved by automatically switching stimulus delivery among 3 electrode pairs oriented at 0, 60 and 120° with a reference axis. Stimuli were triplets of 5-ms voltage pulses applied 5 ms apart (total duration < refractory period). For US, single pulses were applied at only one direction at each run. Using US (monophasic pulses) for successive runs at all directions, mean threshold field (ET) was 3.8 ± 0.1 V/cm. US with 1.2xET at a single direction recruited 38 ± 1% of cells, whereas total US recruitment (the sum of recruitment at the 3 directions without intersection) was 83 ± 2%. With MS (1.2xET), recruitment reached 90 ± 2% ($p<0.05$ vs. single direction US). With biphasic pulses, ET and the stimulus amplitude required for ~90% recruitment were 20-25% lower than with monophasic stimuli ($p<0.05$). Thus the greater efficiency of MS was further enhanced by using biphasic stimuli. Experiments with high-strength pulses at a single direction showed that the field required for lethal injury in 50% of the tested cells (LE50) was 70 ± 2 (N=12) and 81 ± 1 V/cm (N=9) for monophasic and biphasic waveforms, respectively ($p<0.05$). Considering the safety index of electric stimulation as LE50/ET, we conclude that biphasic stimuli are safer (index ~26 vs. 18 for monophasic) because of both lower ET and potency of lethality
(CNPq, CAPES, FAPESP).

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Decreased Inward-rectifier K^+ Current in Myocytes Isolated from a Mouse Model of CPVT

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Catecholamine-induced polymorphic ventricular tachycardia (CPVT) is a highly malignant inherited arrhythmia characterized by adrenergically-mediated bidirectional or polymorphic tachycardia leading to syncope and/or cardiac sudden death. Several mutations in the cardiac sarcoplasmic reticulum (SR) Ca^{2+} release channel (RyR2) with major functional consequences have been identified in human CPVT, which may cause juvenile sudden death induced by stress and exercise. Therefore CPVT showed the first demonstration that not only plasmalemmal but also SR Ca^{2+} channels are crucial in regulating cardiac excitability. The mechanism involved is still unclear and, in addition to the Na^{+}-Ca^{2+} exchanger, plasmalemmal ionic channels could play a role in the triggering of delayed afterdepolarizations. For example, IK1 is an inward rectifying potassium current, present in ventricular myocytes, which contributes to late repolarisation and clamps the resting membrane potential. IK1 down-regulation has been related to longer APD and both early and delayed afterdepolarizations in heart failure. In this work, we investigated the effect of the mutation R4496C of the RyR2 (mouse equivalent of the human R4497C). In freshly isolated cells, we examined IK1 in presence of low and high Ca^{2+} buffering conditions (the pipette contained 50 μM EGTA or 5 mM BAPTA, respectively) using whole cell configuration of voltage-clamp. We found that IK1 is reduced in heterozygous (R4496C +/-) myocytes dialyzed with 50 μM EGTA, as compared to WT cells. Interestingly, when 5 mM BAPTA was present in the pipette solution, IK1 was undistinguishable in R4496C +/- and WT myocytes. Theses results clearly indicate that IK1 is decreased in R4496C +/- and in the absence of fast cytosolic Ca^{2+} buffer. Accordingly, IK1 may be a target of the aberrant activity of RyR2 and may, therefore, actively contribute to the alteration of excitability of CPVT.

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Ventricular Sodium Currents Are Altered In CD4C/HIV Mice

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Cardiac arrhythmias have been reported in HIV patients. Studies have shown that HIV can alter ventricular potassium currents, however, little is known about the effect of HIV on ventricular sodium current (I_{Na}) even though changes in I_{Na} also can lead to rhythm disturbances. Thus, the objective of this study was to characterize the effect of HIV on ventricular I_{Na} in CD4C/HIV mice. These mice exhibit a severe AIDS-like disease. Patch-clamp techniques were used to examine I_{Na} and action potentials (AP) in ventricular myocytes isolated from HIV and wild-type (WT) mice. In HIV myocytes I_{Na} was significantly depressed between -60 and -30 mV (at -50 mV: HIV, -55.3 ± 4.3 pA/pF, n=15; WT, -79.4 ± 5.2 pA/pF, n=16). However, late I_{Na} was similar in both groups (HIV, -4.3 ± 0.4 pA/pF; WT, -4.4 ± 0.4 pA/pF n=22/group). AP amplitude was similar in HIV (90.7 ± 5.1 mV, n=11) and WT (99.8 ± 4 mV, n=15) myocytes, but the maximal velocity of the AP upstroke (V_{max}) was significantly decreased in HIV myocytes (HIV, 54.2 ± 9.6 mV/ms, n=11; WT, 99.2 ± 10.3 mV/ms, n=15). ECG telemetry recordings revealed that the QRS complex was significantly prolonged in HIV mice (HIV, 15.7 ± 0.2 ms, n=22; WT, 14.1 ± 0.5 ms, n=10). Previous studies have shown that elevated levels of cytokines can affect cardiac ion currents. In CD4C/HIV mice serum levels of TNF-alpha are elevated. The present study showed that serum levels of interleukin-1-beta also were elevated in HIV mice (HIV, 18.1 ± 3.1 pg/ml, n=3; WT, 5.1 ± 1.7 pg/ml, n=4). Overall, this study showed that I_{Na} is decreased in HIV ventricular myocytes and that this reduction is likely responsible for the observed prolongation of the QRS complex in HIV mice. These alterations could contribute to the development of cardiac rhythm disturbances.

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Biophysical Characterization of a Novel KCNJ2 Mutation Associated with Andersen-Tawil Syndrome and CPVT Mimicry

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Mutations in KCNJ2, the gene encoding the human inward rectifier potassium channel Kir2.1 (IK1), have been identified in Andersen-Tawil syndrome (ATS). ATS is a multisystem inherited disease exhibiting periodic paralysis, cardiac arrhythmias, and dysmorphic features at times mimicking catecholaminergic polymorphic ventricular tachycardia (CPVT). In this study, we identified a young female presenting with frequent ventricular extrasystoles and